Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(1): 24928
https://doi.org/10.31083/FBL24928

Review

Update on the Progress of Musashi-2 in Malignant Tumors

Yiting Niu[1], Tao Zhou[2], Yanjun Li[1,*]

[1]Department of Hepatobiliary and Pancreatic Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, 030032 Taiyuan, Shanxi, China
[2]Department of Hepatobiliary Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, 030032 Taiyuan, Shanxi, China
*Correspondence: liyjyisheng1017@163.com (Yanjun Li)
Academic Editor: Amancio Carnero Moya
Submitted: 21 May 2024 Revised: 23 July 2024 Accepted: 31 July 2024 Published: 17 January 2025

Abstract

Since the discovery of the Musashi (MSI) protein, its ability to affect the mitosis of Drosophila progenitor cells has garnered significant interest among scientists. In the following 20 years, it has lived up to expectations. A substantial body of evidence has demonstrated that it is closely related to the development, metastasis, migration, and drug resistance of malignant tumors. In recent years, research on the MSI protein has advanced, and many novel viewpoints and drug resistance attempts have been derived; for example, tumor protein p53 mutations and MSI-binding proteins lead to resistance to protein arginine N-methyltransferase 5-targeted therapy in lymphoma patients. Moreover, the high expression of MSI2 in pancreatic cancer might suppress its development and progression. As a significant member of the MSI family, MSI2 is closely associated with multiple malignant tumors, including hematological disorders, common abdominal tumors, and other tumor types (e.g., glioblastoma, breast cancer). MSI2 is highly expressed in the majority of tumors and is related to a poor disease prognosis. However, its specific expression levels and regulatory mechanisms may differ based on the tumor type. This review summarizes the research progress related to MSI2 in recent years, including its occurrence, migration mechanism, and drug resistance, as well as the prospect of developing tumor immunosuppressants and biomarkers.

Keywords: Musashi-2; hepatocellular carcinoma; cancer; epithelial–mesenchymal transition

1. Introduction

Musashi (MSI) was first described in 1994 in a paper investigating the role of asymmetric divisions in sensory organ precursor cells in Drosophila [1]. Loss of the *MSI* gene leads to asymmetric division of Drosophila neuroblasts, ultimately producing a double-bristle phenotype. The gene is called Musashi because of its similarity to the famous fighting sword stance pioneered by the Japanese national hero Miyamoto Musashi. Mammals have two homologous genes of MSI, MSI1 and MSI2, both of which are highly conserved in evolution. The proteins they encode belong to the same family of RNA-binding proteins (RBPs) and participate in mRNA regulation after transcription to regulate gene expression [2]. They primarily target developmental transcription factors and cell cycle regulators, which are also expressed in stem cells (SCs) and are associated with the invasive behavior of tumors [3]. The MSI2 protein has a binding domain and auxiliary domain. The binding domain is located at the N-terminus and is highly conserved among species. The C-terminus is the auxiliary domain, and its protein sequence regulates gene expression by mediating protein–protein interactions to promote or inhibit protein translation [4]. The MSI2 RBP is mainly found in the cytoplasm but can also be found in the nucleoplasm [5].

In the more than 20 years since discovery of the *MSI* gene, progress has been made in many aspects and fields. For example, a study on mouse spermatogonia found that MSI plays a role in spermatogenesis and germline SC development [6]. After knocking out the *MSI2* gene, the division frequency of hematopoietic SCs and progenitor cells was found to be significantly reduced [7]. In a mouse model with MSI2 overexpression, the division frequency of hematopoietic SCs and progenitor cells was significantly increased [8]. In 2003, Barbouti *et al*. [9] first reported that patients with chronic myeloid leukemia (CML) have *MSI2* gene rearrangement, forming the MSI2/homeobox A9 fusion protein; however, the mechanism is unclear. In subsequent years, the role of MSI2 in malignant vascular tumors has been widely confirmed. Overexpression of MSI2 can promote the occurrence and progression of hematological malignancies [10–12]. The occurrence of tumors is related to the abnormal division and differentiation of SCs. MSI2 not only affects the division of SCs but also affects the metastasis of tumors. Therefore, the mechanism of action of MSI2 in multisystem tumors is of great research value, as it could lead to the development of specific tumor-targeted drugs. MSI protein is believed to be highly expressed in tumor cells and is associated with poor differentiation, poor prognosis, lymphatic invasion and metastasis of solid tumors, and expression of other SC markers.

Understanding how MSI regulates cancer-related gene expression under physiological conditions and its possible therapeutic effects requires an understanding of its structure and biochemical functions. MSI belongs to the A/B

type heterogeneous nuclear ribonucleoprotein (hnRNP) with two N-terminal RNA recognition domains (RRMs), of which RRM1 plays a major role and RRM2 is auxiliary. These domains are highly conserved in different species. MSI binds to specific mRNA sequences through these domains, among which interaction with sequences such as ACCUUUUUUUAGAA is preferential. In addition, the C-terminus of MSI contains sequences that interact with other proteins and can affect the translation process. Recent study has also shown that MSI may be involved in regulating Lin-28 homolog A (Lin28A) and affecting the alternative splicing process. Considering its dual regulatory functions and the influence of other proteins on the cellular environment, MSI may exhibit different activities in different cellular environments, which poses a challenge for its potential application in cancer treatment [13].

2. Characteristics of MIS2 in Tumors

2.1 Hematologic Malignancies

Leukemia is a type of malignant clonal disease of hematopoietic SCs. Clonal leukemia cells proliferate and accumulate in large quantities in the bone marrow and other hematopoietic tissues due to mechanisms such as uncontrolled proliferation, differentiation disorders, and blocked apoptosis. The MSI2 protein affects the characteristics of cell division and differentiation. It has been confirmed that it is closely related to the malignant proliferation of hematopoietic SCs in the blood system, and MSI2 is highly expressed in leukemia. In 2010, Ito *et al*. [7] first verified the overexpression of MSI2 in CML using a mouse model. Subsequently, Kharas *et al*. [8] demonstrated that overexpression of MSI2 is a key factor leading to the proliferation and inhibition of apoptosis in myelogenous leukemia (ML) cell lines. In recent years, substantial progress has been made in studying the intrinsic influence mechanism between various types of leukemia and MSI2. The bidirectional combination mechanism of genes and proteins and confirmation of the clear relationship between RBPs and the stemness and proliferation of tumor cells have also helped clarify the role of MSI2-binding proteins in leukemia. At the same time, some novel targets of MSI2-binding proteins have also been discovered, such as the fms-related receptor tyrosine kinase 3 (*FLT3*) gene; with loss of the *MSI2* gene, the protein expression of FLT3 is also down regulated and the apoptosis of leukemia cells is accelerated. This mechanism is relatively unique in the growth process of acute ML (AML) cells [14]. Interleukin 6 cytokine family signal transducer (IL6ST) is a binding and regulatory target of MSI2. IL-6 is a type of IL6ST, which stimulates MSI2 knockdown cells to cause hyperphosphorylation of signal transducer and activator of transcription 3 (STAT3) and extracellular signal-regulated kinase 1/2 (ERK1/2); however, at present, the binding partner of MSI2-binding protein has not been clearly identified [15]. Inhibiting RNA-binding activity is a novel way to treat leukemia. For example, Minuesa *et al*. [16] used molecular chemistry methods to verify that Ro 08-2750 (Ro) can be used as an MSI2 RNA-binding inhibitor. When Ro is reduced and combined with high-affinity chemicals such as nerve growth factor, Ro no longer binds to MSI2, reducing its tumor suppressor effect. This can undoubtedly be used as a new treatment paradigm.

In AML, MSI2 expression is elevated in patients with CCAAT/enhancer-binding protein alpha (CEBPA) mutations. It is worth noting that patients with CEBPA mutations alone have a good prognosis, while the high expression of MSI2 leads to a poor prognosis, which also indicates that other gene mutations affect the expression of MSI2 [17]. Branched-chain amino acid metabolism activated by the MSI2-branched-chain amino acid transaminase 1 (BCAT1) axis promotes cancer progression in ML, and knockdown of MSI2 reduces the levels of BCAT1 protein and phosphorylated p70 S6 kinase [18]. New research methods have also been discovered. For example, Nguyen *et al*. [19] used Hyper Targets of RNA-binding proteins Identified By Editing (HyperTRIBE) to discover that MSI2 RNA-binding activity in leukemia SCs (LSCs) is enhanced and regulated in different ways. An MSI2 mouse model has also been developed to identify LSCs [20]. In chronic lymphocytic leukemia (CLL), MSI2 was found to be upregulated in newly dividing CLL cells [21]; in other cases, it inhibits or induces protein translation to regulate gene expression. These different modes of expression make the mechanism of action of MSI2 more complicated, which is also worth further study and consideration. In MCL cell lines, SRY-box transcription factor 11 (SOX11) directly regulates the transcription of MSI2 in mantle cell lymphoma (MCL) cells; the mRNA and protein expression of MSI2 increases with an increase in SOX11 expression, and conversely decreases [22].

Regarding the therapeutic potential of MSI2 in the hematopoietic and lymphoid system, a study has shown that MSI2 affects the growth and survival of CLL cells and is associated with a poor clinical course and prognosis [21]. In 2017, Vu *et al*. [23] found that synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) and MSI2 share the same mRNA targets and influence each other, making the ribosome network a possible target for leukemia treatment. Subsequently, related chemical drug inhibitors were discovered. For example, quinacrine (QC) can downregulate the expression of MSI2 and upregulate the expression of Numb to induce diffuse large B-cell lymphoma cells to arrest in the G0/G1 cycle [24], and it also has anticancer effects. Using potential MSI2 antagonists to explore traditional Chinese medicine antagonists is also a new approach [25]. The study on chemotherapy resistance have found that MSI2 is an informative biomarker and novel therapeutic target for T-cell acute lymphoblastic leukemia (T-ALL), which can promote the proliferation of T-ALL and promote chemotherapy resistance through the post-transcriptional regulation of Myc [26]. Tumor protein p53 (TP53) mutations and the RBP MSI2 contribute to resistance to protein

Table 1. Expression and Prognosis of MSI2 in Gastrointestinal Malignancies.

Cancer	MSI2 protein expression		Association
	Tumor surrounding the tissue	Tumor tissue	
Hepatocellular carcinoma	-	+	Poor prognosis [28]
Pancreatic cancer	-	+	Poor prognosis [29,31]
Pancreatic ductal adenocarcinoma	-	+	Poor prognosis [30]
Gastric cancer	-	+	Poor prognosis [32]
Breast cancer	-	+	Poor prognosis [33]
Renal cell carcinoma	?	+	Poor prognosis [34]

"+" Significantly high expression; "-" No expression or low expression; "?" unidentified. MSI, Musashi.

arginine N-methyltransferase 5 (PRMT5)-targeted therapy in patients with B-cell lymphoma [27].

2.2 Solid Tumors

MSI2 not only plays a role in the occurrence and development of leukemia and glioblastoma but also has a close relationship with multiple malignant solid tumors, and it can promote or inhibit their occurrence and progression. Solid malignant tumors include primary liver cancer (LC); cholangiocarcinoma; pancreatic, gastric, duodenal, colon, rectal, kidney, ureteral, ovarian, bladder, and adrenal cancers; and malignant lymphoma originating in the abdominal cavity. Due to the relative intractability of solid malignant tumors, it is difficult to obtain specific and effective treatment. In recent years, the correlation between abdominal malignant tumors and MSI2 and its mechanism of action have been frequently mentioned, and related research has also progressed, providing a molecular basis for seeking specific treatment (Table 1, Ref. [28–34]).

2.2.1 Primary LC

In the nearly 10 years since discovery of the *MSI* gene, a study has shown that MSI1 and MSI2 are significantly overexpressed in LC and are not detected in normal liver tissue specimens. However, only the high expression of MSI2 is associated with a poor prognosis. MSI2 may induce the epithelial-mesenchymal transition (EMT). Tumor EMT is closely related to the metastasis and invasion ability of tumors. Knockout of MSI2 significantly reduces the invasion of hepatocellular carcinoma (HCC) cells and changes the expression pattern of epithelial–mesenchymal markers [28]. Together, these results suggest that MSI2 is associated with the EMT and has the potential to be a biomarker for HCC prognosis and invasion; however, the specific mechanism underlying the association between MSI2 and the EMT has not yet been elucidated. The study has explored the mechanism by which MSI2 is affected by various signaling pathways in the tumor EMT. MSI2 indirectly or directly positively regulates epidermal growth factor (EGF), transforming growth factor beta (TGF-β), and Notch and Wnt pathways, thereby affecting the EMT [35]. The plasticity between the EMT and mesenchymal–epithelial transition indicates the feasibility of developing new targets. However, research on these signaling pathways has not been thorough, and MSI2 is not limited to these signaling pathways. Therefore, more research is needed on signaling pathways. The importance of SCs in the occurrence and progression of tumors is self-evident. It has been confirmed that MSI2 is highly expressed in liver cancer stem cells (LCSCs) [36]. Overexpression or knockdown of MSI2 alters the expression of cancer stem cell (CSC)-related genes, self-renewal, and resistance to chemotherapy in HCC cell lines. MSI2 may play a key role in maintaining the stemness and chemotherapy resistance of LCSCs in HCC in an Lin28A-dependent manner. Thus, MSI2 and Lin28A may be used as potential therapeutic targets for eradicating LCSCs. In 2019, one group detected the expression of MSI2 and cluster of differentiation 44 variant 6 (CD44v6) using HCC tissue microarrays and explored the role of MSI2 and Notch1 signaling in CD44v6 LCSCs. Their results showed that MSI2 maintained the stemness of CD44v6 LCSCs by activating Notch1 signaling through interaction with lunatic fringe [37]. The carcinogenic mechanisms of LC are complex and diverse. Myofibroblasts play a key role in the development and progression of HCC. A previous study showed that myofibroblast-specific *MSI2* gene knockout inhibited HCC in mice and conditional deletion of MSI2 in myofibroblasts significantly inhibited the growth of orthotopic transplanted HCC, reduced intrahepatic and lung metastases, and prolonged the overall survival of mice, whereas MSI2 deletion in myofibroblasts reversed these effects [38]. Mechanistically, MSI2 knockout reduced myofibroblast-derived IL-6 and IL-11 secretion by inhibiting the ERK1/2 pathway, thereby attenuating the promotion of CSCs in myofibroblasts. At the same time, the authors showed that knockout of MSI2 in myofibroblasts and the co-knockout of MSI2 in HCC cells could not further attenuate the progression of implanted HCC. In conclusion, myofibroblast-specific MSI2 knockout eliminates the tumor-promoting function of fibroblasts and inhibits the progression of HCC. Thus, targeting myofibroblast MSI2 expression may also be a strategy for future HCC treatment.

In 2021, the study of the SOX2-overlapping transcript (OT) signaling pathway showed that SOX2-OT is highly expressed in HCC cells and tissues, and HCC patients with high SOX2-OT expression have a poor prognosis. Down-

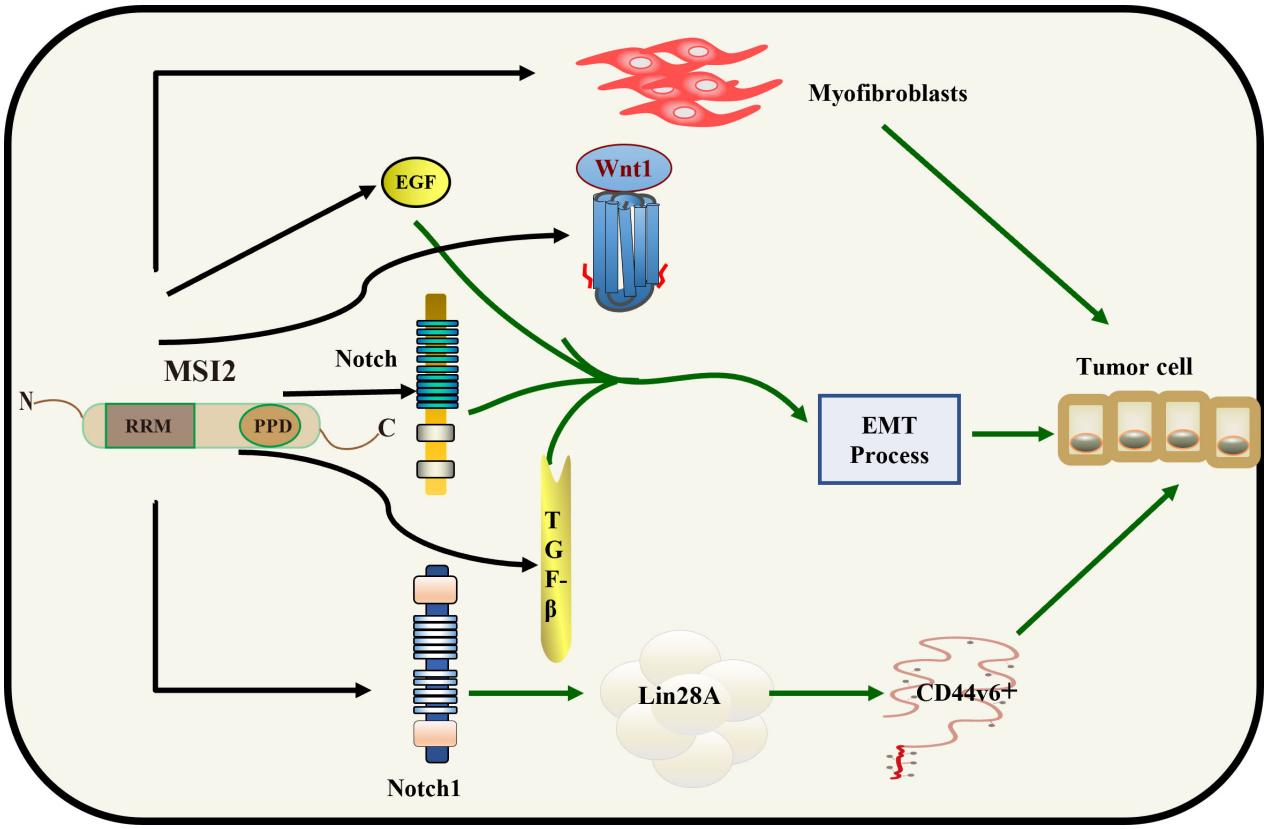

Fig. 1. Mechanistic role of MSI2 in HCC. MSI2 promotes the proliferation of myofibroblasts and directly regulates the EGF, TGF-β, Notch signaling pathway and Wnt1-promoted EMT process, which in turn promotes the proliferation of tumor cells; MSI2 regulates hepatocellular carcinoma SCs. RRM, RNA recognition motif; PPD, protein-protein binding domain; HCC, hepatocellular carcinoma; EGF, epidermal growth factor; TGF-β, transforming growth factor beta; EMT, epithelial-mesenchymal transition; SCs, stem cells; CD44v6, cluster of differentiation 44 variant 6.

regulation of SOX2-OT could inhibit the malignant behavior of HCC cells. SOX2-OT binds to microRNA 143-3p (miR-143-3p) to promote MSI2 expression, and downregulation of miR-143-3p or upregulation of MSI2 could prevent the effects of si-SOX2-OT in HCC cells. SOX2-OT inhibits the targeted inhibition of MSI2 by miR-143-3p through competitive binding with miR-143-3p, thereby promoting the expression of MSI2 and the proliferation, invasion, and migration of HCC cells [39]. The occurrence of HCC is not only related to many signaling pathways but may also be related to the occurrence and progression of pre-existing diseases. It has been shown that the upregulation of MSI2 in hepatitis B virus-related LC is correlated with the expression of β-catenin [40]. It is worth noting that there is relatively little knowledge on the mechanism by which viral hepatitis develops into LC; thus, much research is needed on this topic (Fig. 1).

2.2.2 Pancreatic Cancer

A further understanding of tumor biology and the development of molecular markers detectable in circulation and cancer tissues may underlie the development of new tools to optimize diagnosis and treatment. In gemcitabine-resistant pancreatic cancer (PC), all seven differentially expressed mRNAs (DEmRNAs) have significant effects on cluster of differentiation 4 (CD4) memory T cells, which are affected by the effects of gemcitabine treatment. MSI2 is one of the DEmRNAs that also have significant effects on CD4 effector memory T cells, which predicts a good prognosis [41]. MSI2 promotes chemoresistance and malignant biology in PC by downregulating Numb and p53 [42]. Afterwards, the research group made some first discoveries about MSI2 in the carcinogenic mechanism of PC. The results of the study on MSI2 promoting EGF-induced EMT in PC through zinc finger E-box-binding homeobox 1 (ZEB1)-ERK/mitogen-activated protein kinase (MAPK) signaling showed that EGF enhanced EGF receptor (EGFR) phosphorylation, induced EMT, and activated ZEB1-ERK/MAPK signaling in two PC cell lines. MSI2 silencing reversed the functions of EGF stimulation, including inhibition of EGF-promoted EMT-like cell morphology and EGF-enhanced cell invasion and migration. At the same time, MSI2 silencing inhibited EGF-enhanced EGFR phosphorylation at tyrosine 1068 and reversed EGF-induced EMT and changes in key proteins in ZEB1-ERK/MAPK signaling (ZEB1, E-cadherin, zonula occludens-1, β-catenin, phosphorylated

ERK, and c-Myc), MSI2 promoted EGF-induced EMT in PC *in vivo* through ZEB1-ERK/MAPK signaling, which synergistically promotes the poor prognosis of PC patients [29]. MSI2 is a member of the MSI RBP family and is reported to be an oncoprotein in pancreatic ductal adenocarcinoma (PDAC). The expression of MSI2 is significantly increased in PDAC cell lines and tissues and is positively correlated with poor tumor differentiation, lymph node metastasis, and tumor-node-metastasis stage. Overexpression of MSI2 promotes the proliferation, migration, and invasion of PDAC cells. Further study has shown that MSI2 regulates the hippocampal signaling pathway by directly binding to the mRNA of salvador homolog 1 (SAV1) and Mps one binder 1 (MOB1), and controls the translation and stability of SAV1 and the translation of MOB1. This study shows that MSI2 regulates the hippocampal signaling pathway by inhibiting SAV1 and MOB1 at the post-transcriptional level and promotes PDAC progression [30]. Overexpression of MSI2 contributes to PC progression and drug resistance through negative regulation of Numb and wild-type p53 [43]. Inositol-3-phosphate synthase 1 (ISYNA1) is a new tumor suppressor regulated by MSI2. ISYNA1 silencing promotes cell proliferation and cell cycle by inhibiting p21 and enhances cell migration and invasion by upregulating ZEB1. However, MSI2 silencing upregulates ISYNA1 and p21 but downregulates ZEB1. ISYNA1 silencing significantly antagonizes the reduction in cell migration and invasion caused by MSI2 silencing, indicating that MSI2 promotes the development of PC through a new ISYNA1-p21/ZEB-1 pathway, which provides a new gene-targeted therapy for PC [31] (Fig. 2).

2.2.3 Gastric Cancer

Gastric cancer (GC)-related genes regulating malignant phenotypes are potential therapeutic targets for GC treatment [44]. Currently, MSI2 has been found to be a marker of SCs and progenitor cells, and is closely related to the occurrence and development of tumors. *MSI2* mRNA expression levels are associated with invasion depth, tumor lymph node metastasis stage, degree of differentiation, and tumor size, but not with sex, age, tumor location, or human epidermal growth factor receptor 2 expression [32]. This study showed that increased expression of MSI2 leads to a poor prognosis in GC patients. Although cisplatin drugs have a certain effect on early and late-stage GC, resistance to cisplatin is still an important factor affecting the prognosis of GC. There is increasing evidence that long noncoding RNA is closely related to resistance to chemotherapy drugs. LINC00942 (LNC942) destroying the LNC942-MSI2-c-Myc axis may be a new treatment strategy for GC patients with chemotherapy resistance [45]. *MSI2* mRNA is a prognosis-related gene in GC and is involved in the construction of weighted correlation network analysis, which may also provide new insights into the treatment of GC [46].

2.2.4 Colorectal Cancer

MSI2 is currently considered a potential therapeutic target for a variety of malignant tumors. In 2020, it was discovered that MSI2 may be a predictor of colorectal cancer (CRC) and play an important role in the pathogenesis of CRC [47]. Subsequent study has also confirmed that MSI2 expression increases during CRC progression and is associated with poor prognosis; depletion of MSI2 reduces the growth of CRC cells [48]. MSI2 acts as a relay point, and upstream or downstream regulatory factors targeting MSI2 can be found. It has been found that ubiquitin-specific protease 10 (USP10) can pantothenate MSI2, and after USP10 is knocked out, the proliferation of CRC cells is inhibited [49]. It has also been found that gossypol can be used to develop molecular therapies to modulate MSI1/MSI2 overexpression in CRC [50]. Small molecule bamipines may serve as direct and functional MSI2 antagonists for cancer therapy [51]. TGF-β1 activates the TGF-β/Smad2/3 pathway, stimulates the expression of MSI2, and promotes the progression of CRC [52]. Experiments have shown that overexpression of MSI2 in mice can induce intestinal tumors, but its mechanism has nothing to do with Numb. In human CRC experiments, it was found that MSI2/Numb signaling is closely related to colon SCs that help maintain normal crypt homeostasis, suggesting that the ability to normalize MSI2/Numb signaling by inducing tumor SC differentiation provides a new treatment for CRC [53]. MSI2 expression level may help to establish reasonable treatment selection criteria after colectomy. In addition, there is also a study showing that cytoplasmic MSI2 overexpression may be a biomarker for screening CRC patients for risk of liver metastasis, which helps to identify subgroups of CRC patients with a higher risk of postoperative liver metastasis [54] (Fig. 2).

2.2.5 Bladder Cancer

As early as 2013, data showed that MSI1 was highly and indifferently expressed in both bladder tumor tissue and apparently normal bladder tissue, and when quantitative polymerase chain reaction (PCR) control experiments were performed using primers specific for MSI1 and TATA box-binding protein, MSI1 was found to be expressed at relatively high levels in all tumor and nontumor bladder tissue specimens examined [55]. At present, there is still controversy about the correlation between MSI1 and bladder tumors. In 2016, a detailed study was conducted on the mechanism of MSI2 in the occurrence and development of bladder tumors [12]. The statistical analysis of this study showed that MSI2 expression was significantly correlated with the clinical advanced stage of bladder tumors, lymph node metastasis, and poor prognosis. Overexpression of MSI2 promoted the migration and invasion of bladder cancer (BC) cells. By contrast, knockout of MSI2 inhibited the migration and invasion of BC cells. MSI2 regulates the metastasis and invasion of BC by activating the

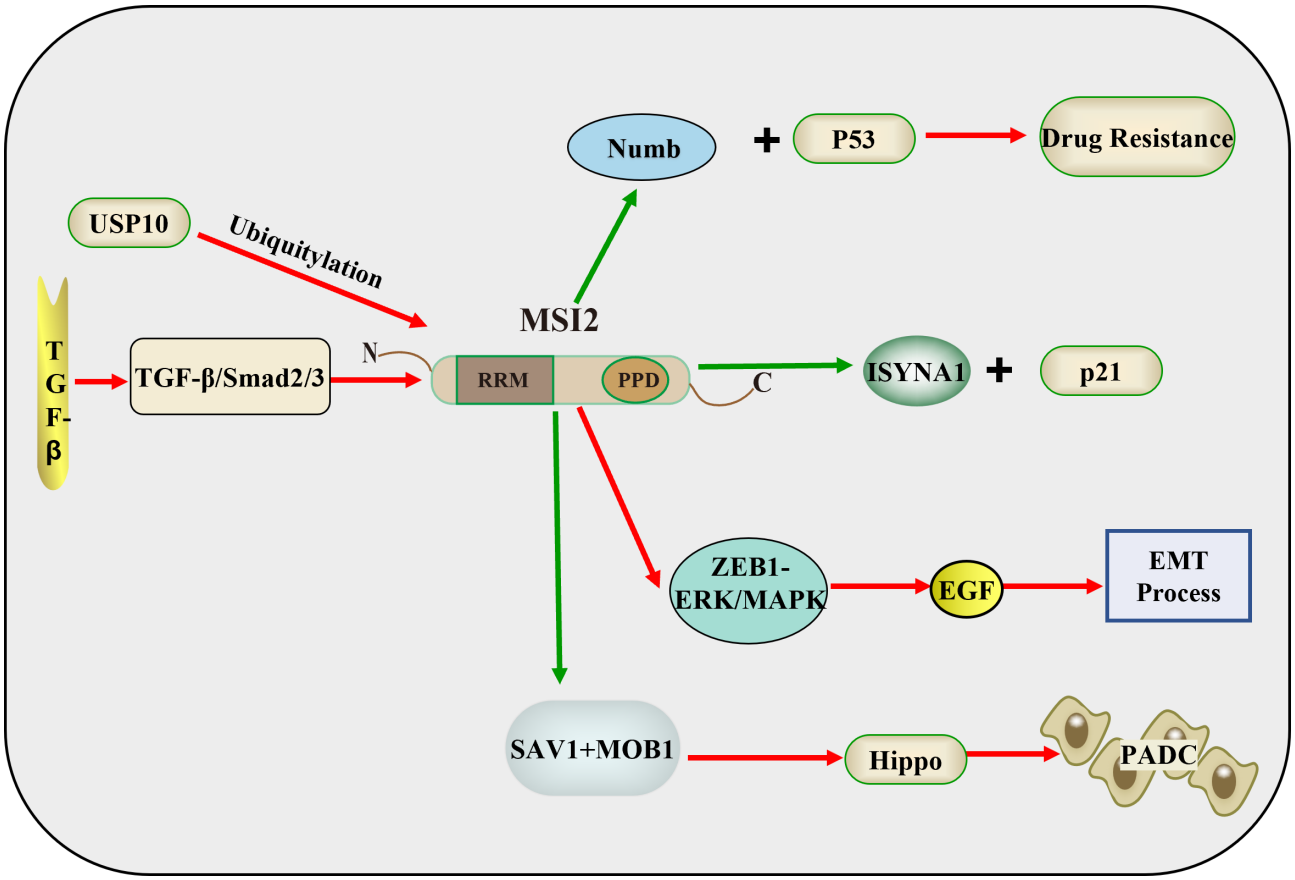

Fig. 2. Mechanistic role of MSI2 in PC and CRC. USP10 promotes MSI2 ubiquitination and the TGF-β/Smad2/3 signaling pathway regulates MSI2 to promote the development of CRC. MSI2 regulates the Numb pathway, p53, ISYNA1, and p21 to promote the proliferation of tumor cells. MSI2 promotes the EMT process and regulates tumor proliferation by regulating the ZEB1-ERK/MAPK signaling pathway. MSI2 directly binds to mRNAs of SAV1 and MOB1 to regulate the Hippo pathway, which promotes the development of PDAC. In the figure, the red line indicates the upward adjustment and the green line indicates the downward adjustment. PC, pancreatic cancer; CRC, colorectal cancer; ISYNA1, Inositol-3-phosphate synthase 1; USP10, ubiquitin-specific protease 10; ZEB1, zinc finger E-box-binding homeobox 1; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; SAV1, salvador homolog 1; MOB1, Mps one binder 1; PDAC, pancreatic ductal adenocarcinoma; RRM, RNA recognition motif; PPD, protein-protein binding domain.

Janus kinase 2 (JAK2)/STAT3 pathway and promoting the expression of JAK2/STAT3 downstream genes in BC. MSI2 may be a valuable prognostic detection marker [33]. Subsequently, in 2018, Zhan *et al.* [56] found that differentiation antagonistic non-protein nodule RNA (DANCR) is mainly distributed in the cytoplasm. DANCR acts as a microRNA (miRNA) sponge, which positively regulates the expression of MSI2 by sponging miR-149, thereby promoting the malignant phenotype of BC cells, thus playing a carcinogenic role in the pathogenesis of BC [56]. MSI2 is an RBP that regulates the stability and translation of certain mRNAs. In 2019, a study showed that synthetic miR-143 negatively regulates the RBP MSI2 in BC cell lines. The study showed that MSI2 positively regulates the expression of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) by directly binding to the target sequence of *KRAS* and promoting its translation [57] (Fig. 3).

2.2.6 Renal Cell Carcinoma

Regarding the treatment of clear cell renal cell carcinoma (ccRCC), with the development of combined therapy in recent years, it has obvious clinical effects; however, patients still do not achieve good treatment effects [58]. With the discovery of MSI2 in other malignant tumors and its potential as a test indicator for malignant tumors, researchers studying renal cancer have also become interested in MSI2. Li *et al.* [59] first discovered that the expression of MSI2 is associated with immune infiltration in advanced ccRCC, especially with CD4 and CD8 T cells. The expression signature of MSI2 can be used as a new indicator to predict the clinical outcomes of patients with advanced ccRCC, and will help us further explore the role of cellular metabolic reprogramming and immune infiltration in advanced ccRCC. In addition, it was innovatively discovered that patients with MSI2 overexpression are more

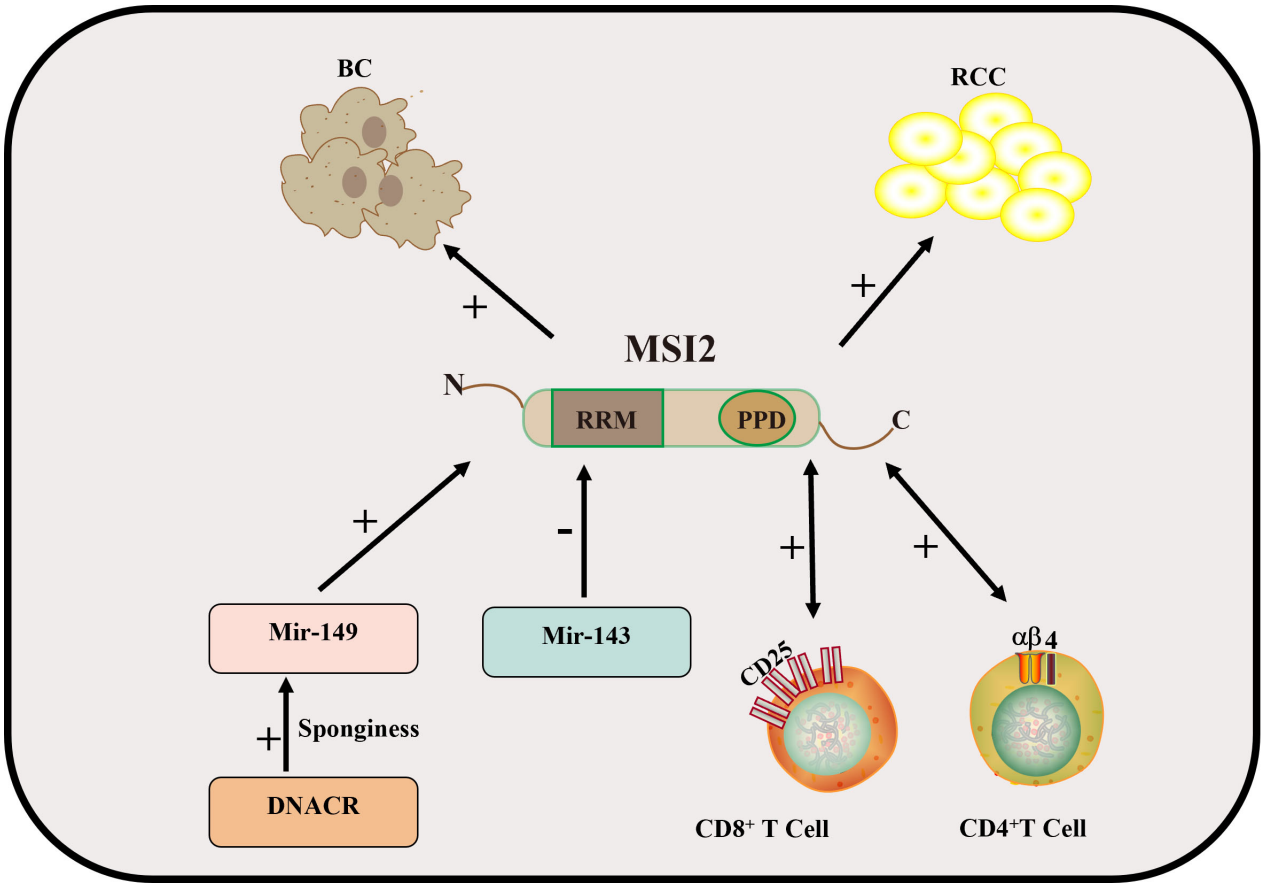

Fig. 3. Mechanism of MSI2 in BC and kidney cancer. In kidney cancer, CD4 and CD8 T cells positively regulate MSI2. MSI2 regulates the JAK2/STAT3 pathway to promote the occurrence and development of BC. MiR-149 and MiR-143 regulate MSI2 to promote the progression of BC. In the figure, "+" indicates an upward adjustment and "-" indicates a downward adjustment. CD4, cluster of differentiation 4; BC, bladder cancer; RCC, renal cell carcinoma; DNACR, differentiation antagonistic non-protein nodal RNA; JAK2/STAT3, Janus tyrosine Kinase 2/Signal Transducer and Activator of Transcription 3.

sensitive to sorafenib, sunitinib, and gefitinib because the expression levels of immunosuppressive factors are very low in these tumors. Adrenocortical carcinoma (ACC) is a rare but highly aggressive adrenocortical cancer with a poor prognosis. Although rare, completely resected ACC has a high risk of recurrence. MSI2 is considered to be a potential prognostic biomarker and therapeutic target for many cancers. The study has also shown that MSI2 has value as a prognostic marker for completely resected ACC and has strengthened research on its role as a possible therapeutic target for patients with ACC [34] (Fig. 3).

2.2.7 Other Related Tumors

With the in-depth study of the mechanism of MSI2 and tumors, it has been found that MSI2 promotes the proliferation and division of tumor cells in other tumors. In lung cancer, it has been confirmed that MSI2 promotes the malignant progression of lung adenocarcinoma (LUAD). ETS variant transcription factor 4 (*ETV4*) gene overexpression directly binds to the promoter region of MSI2 to regulate the transcription of MSI2 [60]. Then it was found that MSI2 protein expression is significantly increased in non-small cell lung cancer (NSCLC) primary tumor samples compared with normal lung tissue [61]. The specific mechanism has also been newly discovered. MSI2 directly binds to the consensus motif in the EGFR mRNA, promoting the translation of the EGFR, thereby promoting the malignant progression of LUAD [62]. MSI2 directly positively regulates Ataxia Telangiectasia Mutated protein expression and the DNA damage response to promote lung cancer [63]. It may also be pathway-related. Krüppel-like factor 4 can significantly inhibit the proliferation, invasion, and migration of NSCLC cells by inhibiting the MSI2/JAK2/STAT3 signaling pathway [64]. The latest study revealed that MSI2 plays an important role in cancer-associated fibroblast-mediated NSCLC cell invasion and metastasis through IL-6 paracrine signaling [65]. The therapeutic effect and drug resistance of MSI2 in lung cancer have also been further studied. Apigenin reprogrammed the alternative splicing of Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) death receptor 5 (DR5) and cellular-FADD-like IL-1β-converting enzyme (FLICE)

inhibitory protein (c-FLIP) by interacting with hnRNPA2 and MSI2, resulting in increased DR5 protein levels and decreased c-FLIP protein levels, thereby enhancing TRAIL-induced apoptosis of primary lung cancer cells [66]. As aforementioned, MSI2 may have clinical value for NSCLC with EGFR mutations, and blocking MSI2 can enhance the activity of targeted inhibitors for NSCLC with *EGFR* gene mutations [62]. Overexpression of MSI2 can make parental cells resistant to gefitinib. In summary, targeting MSI2 in combination with EGFR-tyrosine kinase inhibitors can effectively prevent the emergence of acquired resistance [67].

In breast cancer, MSI2 expression is highly enriched in estrogen receptor (ER)-positive breast cancer. MSI2 alters ESR1 by binding to specific sites in ESR1 RNA and increasing the stability of ESR1 protein, and promotes the progression of ER-positive breast cancer [68]. Choi *et al.* [69] discovered that MSI2 is a novel ubiquitination target protein of deficient breast cancer factor 2 (DBC2), and that MSI2 and DBC2 can directly interact to promote the polyubiquitination and proteasome degradation of MSI2 in breast cancer cells. Subsequent experiments showed that DBC2 can inhibit MSI2-related oncogenic functions and induce cell apoptosis. The expression of MSI2 is significantly downregulated in triple-negative breast cancer (TNBC) tissues. MSI2a is a functional isoform of MSI2. Its expression inhibits the invasion of TNBC by stabilizing *TP53INP1* mRNA and inhibiting the activity of ERK1/2 [70]. MSI-binding proteins are dysregulated in inflammatory breast cancer and are associated with tumor proliferation, CSC phenotype, and radio resistance [71].

In glioma, the positive feedback loop of MSI2-TGFβ/SMAD3 signaling activates EMT and methylguanine methyltransferase [72]. In the latest study, the MSI2 metabolism-related mechanism is more prominent, and the MSI2/small nucleolar RNA, C/D box 12B/FIP1L1/zinc finger and Broad-complex, Tramtrack, and Bric-a-brac (BTB) domain containing 4-positive feedback loop can regulate the glucose and lipid metabolism of glioblastoma cells [73]. Subsequently, another sugar metabolism pathway related to the migration, invasion, and proliferation of neuroblastoma cells was discovered. MSI2 promotes the pentose phosphate pathway by activating c-Myc-glucose-6-phosphate dehydrogenase signaling [74]. In osteosarcoma, when miR-149 is overexpressed, MSI2 protein expression is significantly downregulated. When miR-149 is silenced, MSI2 protein is significantly upregulated [75].

In recent years, the study has found that MSI2 is also expressed in ovarian cancer (OC), and its mRNA-binding protein is highly expressed in cervical cancer (CC) tissues, leading to a poor prognosis [76]. The mechanism may be that MSI2 promotes CC cell growth, invasiveness, and spheroid formation by directly binding to c-Fos mRNA and increasing c-Fos protein expression. In this study, it was also found that p53 can reduce the expression of MSI2 by increasing the level of miR-143/miR-107, thereby reducing the poor prognosis. There are also studies showing that MIR4435-2HG knockout inhibits CC cell proliferation, migration, and invasion by regulating the miR-128-3p/MSI2 axis [77]. miR-149 exerts anti-OC effect by regulating MSI2 through phosphoinositide 3-kinase (PI3K)/AKT [78]. In general, the study of miRNA provides a possible treatment strategy and a new research direction for CC.

We have delineated the expression and role of the *MSI2* gene and regulatory protein in diverse tumors; however, certain disparities exist concurrently. For example, the expression of MSI2 in leukemia and abdominal malignancies exhibits the following similarities and dissimilarities. There is high expression of MSI2 in leukemia, particularly AML, and the expression of MSI2 is frequently clearly elevated and is associated with adverse disease progression and prognosis. The expression of MSI2 in abdominal malignancies demonstrates variability; for example, in LC, PC, GC, and CRC, there is a certain degree of variation in the expression level of MSI2. Moreover, in some types of abdominal tumors, the expression of MSI2 is also significantly augmented and is associated with the malignancy degree of the tumors and poor prognosis. The role of MSI2 in leukemia cells primarily encompasses maintaining the self-renewal of leukemia SCs and promoting cell proliferation, and influencing cell proliferation by regulating several signaling pathways including the STAT3 and ERK1/2 signaling pathways. The role of MSI2 in abdominal malignancies involves promoting the proliferation, migration, and invasion ability of tumor cells, as well as maintaining the properties of CSCs, which also operates by regulating multiple signaling pathways such as Notch, Wnt, and Hippo. MSI2 has been less investigated in abdominal malignancies compared to leukemia, but existing research indicates that MSI2 might be an important regulator and potential therapeutic target for these tumors.

Although MSI2 is highly expressed in both leukemia and abdominal malignancy and is associated with a poor disease prognosis, its specific expression level and regulatory mechanism may vary with different tumor types. In leukemia, MSI2 is mainly related to the maintenance of SCs and cell proliferation, while in abdominal malignancies, MSI2 may be more implicated in the proliferation, migration, and invasion of tumor cells. Overall, the role of MSI2 in these diseases renders it an important subject of study and potential therapeutic target.

3. Conclusions

In the human body, MSI2 affects the occurrence and progression of a variety of tumors, it encompasses diseases of the blood system and common solid tumors in the abdomen such as leukemia, lymphoma, HCC, PC, kidney cancer, stomach cancer, glioblastoma, breast cancer, tumors of the female reproductive system, lung cancer, and CRC. In leukemia, MSI2 primarily maintains the self-renewal of leukemia SCs and promotes cell proliferation and influ-

ences the cell cycle by regulating signaling pathways. In lymphoma, MSI2 can facilitate the proliferation of T-ALL through post-transcriptional regulation of Myc, and in combination with TP53 mutants, leads to drug resistance in patients with B-cell lymphoma. High expression of MSI2 leads to poor prognosis of HCC, CRC, GC, BC, and renal cancer, while high expression of MSI2 in PC may inhibit the occurrence and development of cancer. In liver cancer, MSI2 affects the occurrence and progression of cancer by regulating the EGF, TGF, Notch and Wnt pathways to promote the EMT process, but the specific mechanism is still unclear. In PC, MSI2 is regulated through various pathways, thereby promoting the EMT pathway or affecting the drug resistance and poor prognosis of tumors. Studies have also demonstrated that a high expression level of MSI2 in PC results in a more favorable prognosis. In CRC and BC, MSI2 can serve as an intermediate target for upstream regulation, thereby regulating downstream pathways. All of these indicate that the process of cancer occurrence and development can be affected by controlling MSI2, and it may also serve as a specific marker for tumor detection, prognosis, and recurrence. Of course, there are still many areas that have not been clearly elucidated, and it still has great potential research value.

In summary, the research progress on MSI2 has a clear relationship with the proliferation and differentiation of cancer, and affects the drug resistance and stemness of various malignant tumors. Its mechanism not only acts on the *MSI2* gene coding sequence (e.g., MSI2 directly binds to the consensus motif in EGFR mRNA, promotes EGFR translation, and thus promotes the malignant progression of LUAD), and acts on its transcribed mRNA (e.g., in OC, MSI2 promotes CC cell growth, invasiveness, and globular formation by directly binding to c-Fos mRNA and increasing c-FOS protein expression), and is more likely to act on the ribosome (e.g., SYNCRIP and MSI2 share the same ribosome network target and influence each other). MSI2 indirectly or directly affects the synthesis of small molecules to regulate pathways, and ultimately affects the division of tumor cells, or affects the migration and invasion of tumors by acting on the EMT. These can prove the feasibility of using MSI2 as a target, and unique molecular inhibitors can be developed for different mechanisms and pathways in each tumor. However, it is worth mentioning that in the process of tumor migration and metastasis, the only clear mechanism of action may be EMT, and the mechanism affecting distant metastasis has not yet been elucidated. Better research methods may obtain previously undiscovered mechanisms, such as network data analysis, and we also look forward to technological innovations in *MSI2* gene research.

The mechanism of MSI2 resistance to tumors has been extensively studied. For example, TP53 mutations and MSI2 binding proteins induce lymphoma patients to develop resistance to PRMT5 targeted therapy. The RBP MSI2 sustains the growth and leukemogenic potential of MLL-rearranged ALL, and is involved in glucocorticoid resistance [79]. However, it seems that drug inhibitors based on the action of MSI2 are still in the theoretical stage. For example, QC can downregulate the expression of MSI2 and upregulate the expression of Numb to induce lymphoma cells to stagnate in the G0/G1 division cycle, but clinical trials have not yet been conducted for verification. The findings described above show that the regulatory mechanism of MSI2 in various tumors span several signaling pathways. Key signaling pathways include the classic Notch signaling pathway, Wnt/β-catenin signaling pathway, TGF-β signaling pathway, MAPK/ERK signaling pathway, Hippo signaling pathway, and PI3K/AKT signaling pathway [7,80–82]. MSI2 can promote the activity of Notch signaling pathway by regulating mRNA stability and translation efficiency of Notch receptor. The Notch signaling pathway plays an important role in a variety of cancers, such as leukemia and solid tumors. MSI2 mainly affects the maintenance of tumor SCs and cancer progression in the Wnt/β-catenin signaling pathway. MSI2 can promote cell growth and survival by affecting the expression of key genes in the PI3K/AKT signaling pathway, which is found to be activated in many cancer types. MSI2 may influence cell proliferation and differentiation by regulating gene expression related to the MAPK/ERK pathway. Abnormal activation of the MAPK/ERK pathway is associated with the high expression of MSI2 in a variety of cancers. To target these signaling pathways, researchers are also trying to develop inhibitors, gene therapies, and targeted drugs. Small molecule inhibitors or RNA interference (RNAi) molecules that inhibit MSI2 to reduce MSI2 expression or block its function have also been used to study MSI2. For example, Ro 08-2750, a specific inhibitor of MSI2, has been studied to reduce the survival rate of tumor cells. Some approaches that have been implemented include developing antibody-drug conjugates targeting MSI2 to kill cancer cells by binding to MSI2 and releasing cytotoxic drugs, and combining MSI2 inhibitors with existing cancer therapies such as chemotherapy, radiation, or other targeted drugs to enhance the therapeutic effect. In addition, CRISPR/Cas9 and other gene editing technology have been used to directly knock out or modify the *MSI2* gene to study its disease-causing role in cancer. Although there have been many studies on drug resistance, the lack of clinical trials has prevented the transformation of drug resistance and the development of inhibitors from obtaining innovative and valuable ideas.

Under the influence of these mechanisms, the clinical treatment of these cancer patients should be personalized and combined. In early cancer diagnosis, MSI2 exhibits potential due to its involvement in maintaining cancer cell stemness and proliferation. This encompasses the utilization of circulating tumor DNA (ctDNA) and miRNA as biomarkers, providing minimally invasive options for detecting cancer-related genetic and molecular alterations, thereby enhancing early detection rates and patient out-

comes. Platforms for miRNA assays and quantitative real-time polymerase chain reaction (qPCR) strategies have been developed to quantify miRNAs in clinical samples with the aim of identifying reliable biomarkers for early cancer screening [83]. According to the results of the MSI2 expression level in patients, personalized treatment may be developed; for example, patients with high MSI2 expression may be more sensitive to specific MSI2 inhibitors or combination therapy. To monitor the treatment effect, the expression of MSI2 before and after treatment can be detected. In addition to conventional anticancer chemotherapy drug therapy, some other targeted therapy strategies are also considered to be promising; for example, developing specific monoclonal antibodies against MSI2 protein to inhibit its function by blocking the binding of MSI2 to its RNA target. Specific anti-MSI2 antibodies can also be combined with cytotoxic drugs to target and kill cancer cells that express MSI2. RNAi is a good method in which small interfering RNAs are designed to specifically target *MSI2* mRNA and degrade *MSI2* mRNA through RNAi to reduce its expression. Short hairpin RNA is expressed using gene vectors that continuously interfere with *MSI2* gene expression. Antisense oligonucleotides bind to *MSI2* mRNA and prevent its translation, thus downregulating MSI2 protein expression.

In the above malignant tumors, MSI2 directly or indirectly regulates the occurrence and development of tumors, and its high expression is closely related to the poor prognosis of many cancers. MSI2 has great potential as a specific detection index for early tumor screening and diagnosis. Its high specificity and sensitivity make it expected to become an important tool in precision medicine, contributing to the early detection and accurate diagnosis of tumors, especially in noninvasive detection methods such as liquid biopsy, MSI2 has a particularly broad application prospect. At the same time, targeted therapy strategies for MSI2 also show high research value. Targeting MSI2 through various means such as small molecule inhibitors, antibody drugs, and RNAi is expected to significantly inhibit the growth and metastasis of tumor cells, thereby improving the efficacy of tumor therapy. To summarize, the versatility of MSI2 and key role in tumor biology make it a hot spot in tumor research. Future studies should continue to explore the molecular mechanism and clinical application potential of MSI2; promote its application in tumor screening, diagnosis, and treatment; and ultimately achieve accurate diagnosis and personalized treatment of tumor patients. This will lead to revolutionary breakthroughs in cancer research and clinical practice, and create a new era of cancer treatment.

Abbreviations

ACC, Adrenocortical carcinoma; BC, Bladder Cancer; CML, Chronic myelogenous leukemia; CSCs, Cancer stem cells; CRC, Colorectal cancer; DANCR, Differentiation antagonistic non-protein nodal RNA; EGF, Epidermal growth factor; EMT, Epithelial–Mesenchymal Transition; GC, Gastric cancer; HC, Hepatocellular carcinoma; ISYNA1, Inositol-3-phosphate synthase 1; MSI, Musashi; MSI1, Musashi-1; MSI2, Musashi-2; PC, Pancreatic cancer; PDAC, Pancreatic ductal adenocarcinoma; RCC, Renal cell carcinoma; TGF-β1, Transforming growth factor beta-1; USP10, Ubiquitin-specific protease 10.

Author Contributions

YTN and YJL designed the research study. YTN and TZ searching and collating literature. YTN drawing figures. YTN, TZ and YJL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We gratefully acknowledge the assistance and instruction from Dr Rui Li and Dr Panpan Zheng of the Third Hospital of Shanxi Medical University.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Nakamura M, Okano H, Blendy JA, Montell C. Musashi, a neural RNA-binding protein required for Drosophila adult external sensory organ development. Neuron. 1994; 13: 67–81.

[2] Okano H, Imai T, Okabe M. Musashi: a translational regulator of cell fate. Journal of Cell Science. 2002; 115: 1355–1359.

[3] Byers RJ, Currie T, Tholouli E, Rodig SJ, Kutok JL. MSI2 protein expression predicts unfavorable outcome in acute myeloid leukemia. Blood. 2011; 118: 2857–2867.

[4] Han SP, Tang YH, Smith R. Functional diversity of the hnRNPs: past, present and perspectives. The Biochemical Journal. 2010; 430: 379–392.

[5] Clarke RB, Spence K, Anderson E, Howell A, Okano H, Potten CS. A putative human breast stem cell population is enriched for steroid receptor-positive cells. Developmental Biology. 2005; 277: 443–456.

[6] Siddall NA, McLaughlin EA, Marriner NL, Hime GR. The RNA-binding protein Musashi is required intrinsically to maintain stem cell identity. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 8402–8407.

[7] Ito T, Kwon HY, Zimdahl B, Congdon KL, Blum J, Lento WE, *et al*. Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature. 2010; 466: 765–768.

[8] Kharas MG, Lengner CJ, Al-Shahrour F, Bullinger L, Ball B, Zaidi S, *et al*. Musashi-2 regulates normal hematopoiesis and

promotes aggressive myeloid leukemia. Nature Medicine. 2010; 16: 903–908.

[9] Barbouti A, Höglund M, Johansson B, Lassen C, Nilsson PG, Hagemeijer A, *et al*. A novel gene, MSI2, encoding a putative RNA-binding protein is recurrently rearranged at disease progression of chronic myeloid leukemia and forms a fusion gene with HOXA9 as a result of the cryptic t(7;17)(p15;q23). Cancer Research. 2003; 63: 1202–1206.

[10] Zhao HZ, Jia M, Luo ZB, Cheng YP, Xu XJ, Zhang JY, *et al*. Prognostic significance of the Musashi-2 (MSI2) gene in childhood acute lymphoblastic leukemia. Neoplasma. 2016; 63: 150–157.

[11] Mu Q, Wang Y, Chen B, Qian W, Meng H, Tong H, *et al*. High expression of Musashi-2 indicates poor prognosis in adult B-cell acute lymphoblastic leukemia. Leukemia Research. 2013; 37: 922–927.

[12] Taggart J, Ho TC, Amin E, Xu H, Barlowe TS, Perez AR, *et al*. MSI2 is required for maintaining activated myelodysplastic syndrome stem cells. Nature Communications. 2016; 7: 10739.

[13] Zou H, Luo J, Guo Y, Liu Y, Wang Y, Deng L, *et al*. RNA-binding protein complex LIN28/MSI2 enhances cancer stem cell-like properties by modulating Hippo-YAP1 signaling and independently of Let-7. Oncogene. 2022; 41: 1657–1672.

[14] Hattori A, McSkimming D, Kannan N, Ito T. RNA binding protein MSI2 positively regulates FLT3 expression in myeloid leukemia. Leukemia Research. 2017; 54: 47–54.

[15] Duggimpudi S, Kloetgen A, Maney SK, Münch PC, Hezaveh K, Shaykhalishahi H, *et al*. Transcriptome-wide analysis uncovers the targets of the RNA-binding protein MSI2 and effects of MSI2's RNA-binding activity on IL-6 signaling. The Journal of Biological Chemistry. 2018; 293: 15359–15369.

[16] Minuesa G, Albanese SK, Xie W, Kazansky Y, Worroll D, Chow A, *et al*. Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. Nature Communications. 2019; 10: 2691.

[17] Heyes E, Schmidt L, Manhart G, Eder T, Proietti L, Grebien F. Identification of gene targets of mutant C/EBPα reveals a critical role for MSI2 in CEBPA-mutated AML. Leukemia. 2021; 35: 2526–2538.

[18] Hattori A, Tsunoda M, Konuma T, Kobayashi M, Nagy T, Glushka J, *et al*. Cancer progression by reprogrammed BCAA metabolism in myeloid leukaemia. Nature. 2017; 545: 500–504.

[19] Nguyen DTT, Lu Y, Chu KL, Yang X, Park SM, Choo ZN, *et al*. HyperTRIBE uncovers increased MUSASHI-2 RNA binding activity and differential regulation in leukemic stem cells. Nature Communications. 2020; 11: 2026.

[20] Spinler K, Bajaj J, Ito T, Zimdahl B, Hamilton M, Ahmadi A, *et al*. A stem cell reporter based platform to identify and target drug resistant stem cells in myeloid leukemia. Nature Communications. 2020; 11: 5998.

[21] Palacios F, Yan XJ, Ferrer G, Chen SS, Vergani S, Yang X, *et al*. Musashi 2 influences chronic lymphocytic leukemia cell survival and growth making it a potential therapeutic target. Leukemia. 2021; 35: 1037–1052.

[22] Sureda-Gómez M, Balsas P, Rodríguez ML, Nadeu F, De Bolòs A, Eguileor Á, *et al*. Tumorigenic role of Musashi-2 in aggressive mantle cell lymphoma. Leukemia. 2023; 37: 408–421.

[23] Vu LP, Prieto C, Amin EM, Chhangawala S, Krivtsov A, Calvo-Vidal MN, *et al*. Functional screen of MSI2 interactors identifies an essential role for SYNCRIP in myeloid leukemia stem cells. Nature Genetics. 2017; 49: 866–875.

[24] Yang S, Sheng L, Xu K, Wang Y, Zhu H, Zhang P, *et al*. Anticancer effect of quinacrine on diffuse large B cell lymphoma via inhibition of MSI2 NUMB signaling pathway. Molecular Medicine Reports. 2018; 17: 522–530.

[25] Adeniyi JN, Adeniyi AA, Moodley R, Nlooto M, Ngcobo M, Gomo E, *et al*. Unravelling the drugability of MSI2 RNA recognition motif (RRM) protein and the prediction of their effective antileukemia inhibitors from traditional herb concoctions. Journal of Biomolecular Structure & Dynamics. 2022; 40: 2516–2529.

[26] Zhang J, Duan Y, Wu P, Chang Y, Wang Y, Hu T, *et al*. Clonal evolution dissection reveals that a high MSI2 level promotes chemoresistance in T-cell acute lymphoblastic leukemia. Blood. 2024; 143: 320–335.

[27] Erazo T, Evans CM, Zakheim D, Chu KL, Refermat AY, Asgari Z, *et al*. TP53 mutations and RNA-binding protein MUSASHI-2 drive resistance to PRMT5-targeted therapy in B-cell lymphoma. Nature Communications. 2022; 13: 5676.

[28] He L, Zhou X, Qu C, Hu L, Tang Y, Zhang Q, *et al*. Musashi2 predicts poor prognosis and invasion in hepatocellular carcinoma by driving epithelial-mesenchymal transition. Journal of Cellular and Molecular Medicine. 2014; 18: 49–58.

[29] Sheng W, Shi X, Lin Y, Tang J, Jia C, Cao R, *et al*. Musashi2 promotes EGF-induced EMT in pancreatic cancer via ZEB1-ERK/MAPK signaling. Journal of Experimental & Clinical Cancer Research: CR. 2020; 39: 16.

[30] Yang H, Hu J, Chen J, Chen Z, Jiao F, Cui J, *et al*. RNA-binding protein Musashi2 regulates Hippo signaling via SAV1 and MOB1 in pancreatic cancer. Medical Oncology (Northwood, London, England). 2020; 37: 84.

[31] Zhou L, Sheng W, Jia C, Shi X, Cao R, Wang G, *et al*. Musashi2 promotes the progression of pancreatic cancer through a novel ISYNA1-p21/ZEB-1 pathway. Journal of Cellular and Molecular Medicine. 2020; 24: 10560–10572.

[32] Yang Z, Li J, Shi Y, Li L, Guo X. Increased musashi 2 expression indicates a poor prognosis and promotes malignant phenotypes in gastric cancer. Oncology Letters. 2019; 17: 2599–2606.

[33] Yang C, Zhang W, Wang L, Kazobinka G, Han X, Li B, *et al*. Musashi-2 promotes migration and invasion in bladder cancer via activation of the JAK2/STAT3 pathway. Laboratory Investigation; a Journal of Technical Methods and Pathology. 2016; 96: 950–958.

[34] Veronez LC, das Chagas PF, Corrêa CAP, Baroni M, da Silva KR, Nagano LF, *et al*. MSI2 expression in adrenocortical carcinoma: Association with unfavorable prognosis and correlation with steroid and immune-related pathways. Journal of Cellular Biochemistry. 2021; 122: 1925–1935.

[35] Sun J, Sheng W, Ma Y, Dong M. Potential Role of Musashi-2 RNA-Binding Protein in Cancer EMT. OncoTargets and Therapy. 2021; 14: 1969–1980.

[36] Fang T, Lv H, Wu F, Wang C, Li T, Lv G, *et al*. Musashi 2 contributes to the stemness and chemoresistance of liver cancer stem cells via LIN28A activation. Cancer Letters. 2017; 384: 50–59.

[37] Wang X, Wang R, Bai S, Xiong S, Li Y, Liu M, *et al*. Musashi2 contributes to the maintenance of CD44v6+ liver cancer stem cells via notch1 signaling pathway. Journal of Experimental & Clinical Cancer Research: CR. 2019; 38: 505.

[38] Qu C, He L, Yao N, Li J, Jiang Y, Li B, *et al*. Myofibroblast-Specific Msi2 Knockout Inhibits HCC Progression in a Mouse Model. Hepatology (Baltimore, Md.). 2021; 74: 458–473.

[39] Zhao H, Bi M, Lou M, Yang X, Sun L. Downregulation of SOX2-OT Prevents Hepatocellular Carcinoma Progression Through miR-143-3p/MSI2. Frontiers in Oncology. 2021; 11: 685912.

[40] Wang MH, Qin SY, Zhang SG, Li GX, Yu ZH, Wang K, *et al*. Musashi-2 promotes hepatitis Bvirus related hepatocellular carcinoma progression via the Wnt/β-catenin pathway. American Journal of Cancer Research. 2015; 5: 1089–1100.

[41] Gu J, Zhang J, Huang W, Tao T, Huang Y, Yang L, *et al*. Activating miRNA-mRNA network in gemcitabine-resistant pancreatic cancer cell associates with alteration of memory $CD4^+$ T cells.

Annals of Translational Medicine. 2020; 8: 279.
[42] Sheng W, Dong M, Chen C, Li Y, Liu Q, Dong Q. Musashi2 promotes the development and progression of pancreatic cancer by down-regulating Numb protein. Oncotarget. 2017; 8: 14359–14373.
[43] Sheng W, Dong M, Wang G, Shi X, Gao W, Wang K, *et al*. The diversity between curatively resected pancreatic head and body-tail cancers based on the 8th edition of AJCC staging system: a multicenter cohort study. BMC Cancer. 2019; 19: 981.
[44] Wang Z, Tang F, Qi G, Yuan S, Zhang G, Tang B, *et al*. KDM5B is overexpressed in gastric cancer and is required for gastric cancer cell proliferation and metastasis. American Journal of Cancer Research. 2014; 5: 87–100.
[45] Zhu Y, Zhou B, Hu X, Ying S, Zhou Q, Xu W, *et al*. LncRNA LINC00942 promotes chemoresistance in gastric cancer by suppressing MSI2 degradation to enhance c-Myc mRNA stability. Clinical and Translational Medicine. 2022; 12: e703.
[46] Zheng X, Wang X, Zheng L, Zhao H, Li W, Wang B, *et al*. Construction and Analysis of the Tumor-Specific mRNA-miRNA-lncRNA Network in Gastric Cancer. Frontiers in Pharmacology. 2020; 11: 1112.
[47] Fan X, Liu L, Shi Y, Guo F, Wang H, Zhao X, *et al*. Integrated analysis of RNA-binding proteins in human colorectal cancer. World Journal of Surgical Oncology. 2020; 18: 222.
[48] Kharin L, Bychkov I, Karnaukhov N, Voloshin M, Fazliyeva R, Deneka A, *et al*. Prognostic role and biologic features of Musashi-2 expression in colon polyps and during colorectal cancer progression. PloS One. 2021; 16: e0252132.
[49] Ouyang SW, Liu TT, Liu XS, Zhu FX, Zhu FM, Liu XN, *et al*. USP10 regulates Musashi-2 stability via deubiquitination and promotes tumour proliferation in colon cancer. FEBS Letters. 2019; 593: 406–413.
[50] Lan L, Liu H, Smith AR, Appelman C, Yu J, Larsen S, *et al*. Natural product derivative Gossypolone inhibits Musashi family of RNA-binding proteins. BMC Cancer. 2018; 18: 809.
[51] Zhang X, Su K, Liu Y, Zhu D, Pan Y, Ke X, *et al*. Small Molecule Palmatine Targeting Musashi-2 in Colorectal Cancer. Frontiers in Pharmacology. 2022; 12: 793449.
[52] Yu ZL, Liu J, Ning ZK, Tian HK, Wu X, Huang YF, *et al*. The TGF-β/Smad$_{2/3}$ signaling pathway is involved in Musashi2-induced invasion and metastasis of colorectal cancer. Molecular Carcinogenesis. 2023; 62: 261–276.
[53] Opdenaker LM, Kowash R, Masters G, Boman BM, Zhang T, Modarai SR. Increased Musashi-2 and Decreased NUMB Protein Levels Observed in Human Colorectal Cancer are reverted to Normal Levels by ATRA-Induced Cell Differentiation. International Journal of Cancer Research & Therapy. 2018; 3: 10.33140/ijcrt/03/02/00003.
[54] Zong Z, Zhou T, Rao L, Jiang Z, Li Y, Hou Z, *et al*. Musashi2 as a novel predictive biomarker for liver metastasis and poor prognosis in colorectal cancer. Cancer Medicine. 2016; 5: 623–630.
[55] Nikpour P, Mowla SJ, Forouzandeh-Moghaddam M, Ziaee SA. The stem cell self-renewal gene, Musashi 1, is highly expressed in tumor and non-tumor samples of human bladder. Indian Journal of Cancer. 2013; 50: 214–218.
[56] Zhan Y, Chen Z, Li Y, He A, He S, Gong Y, *et al*. Long non-coding RNA DANCR promotes malignant phenotypes of bladder cancer cells by modulating the miR-149/MSI2 axis as a ceRNA. Journal of Experimental & Clinical Cancer Research: CR. 2018; 37: 273.
[57] Tsujino T, Sugito N, Taniguchi K, Honda R, Komura K, Yoshikawa Y, *et al*. MicroRNA-143/Musashi-2/KRAS cascade contributes positively to carcinogenesis in human bladder cancer. Cancer Science. 2019; 110: 2189–2199.
[58] Chen YW, Rini BI, Beckermann KE. Emerging Targets in Clear Cell Renal Cell Carcinoma. Cancers. 2022; 14: 4843.
[59] Li H, Meng X, You X, Zhou W, Ouyang W, Pu X, *et al*. Increased expression of the RNA-binding protein Musashi-2 is associated with immune infiltration and predicts better outcomes in ccRCC patients. Frontiers in Oncology. 2022; 12: 949705.
[60] Cheng T, Zhang Z, Cheng Y, Zhang J, Tang J, Tan Z, *et al*. ETV4 promotes proliferation and invasion of lung adenocarcinoma by transcriptionally upregulating MSI2. Biochemical and Biophysical Research Communications. 2019; 516: 278–284.
[61] Topchu I, Karnaukhov N, Mazitova A, Yugai V, Voloshin M, Tikhomirova M, *et al*. Musashi 2 (MSI2) expression as an independent prognostic biomarker in non-small cell lung cancer (NSCLC). Journal of Thoracic Disease. 2021; 13: 1370–1379.
[62] Makhov P, Bychkov I, Faezov B, Deneka A, Kudinov A, Nicolas E, *et al*. Musashi-2 (MSI2) regulates epidermal growth factor receptor (EGFR) expression and response to EGFR inhibitors in EGFR-mutated non-small cell lung cancer (NSCLC). Oncogenesis. 2021; 10: 29.
[63] Bychkov I, Deneka A, Topchu I, Pangeni RP, Lengner C, Karanicolas J, *et al*. Musashi-2 (MSI2) regulation of DNA damage response in lung cancer. bioRxiv. 2024. (preprint)
[64] Luo DD, Zhao F. KLF4 suppresses the proliferation and metastasis of NSCLC cells via inhibition of MSI2 and regulation of the JAK/STAT3 signaling pathway. Translational Oncology. 2022; 22: 101396.
[65] Samart P, Heenatigala Palliyage G, Issaragrisil S, Luanpitpong S, Rojanasakul Y. Musashi-2 in cancer-associated fibroblasts promotes non-small cell lung cancer metastasis through paracrine IL-6-driven epithelial-mesenchymal transition. Cell & Bioscience. 2023; 13: 205.
[66] Voss OH, Arango D, Tossey JC, Villalona Calero MA, Doseff AI. Splicing reprogramming of TRAIL/DISC-components sensitizes lung cancer cells to TRAIL-mediated apoptosis. Cell Death & Disease. 2021; 12: 287.
[67] Yiming R, Takeuchi Y, Nishimura T, Li M, Wang Y, Meguro-Horike M, *et al*. MUSASHI-2 confers resistance to third-generation EGFR-tyrosine kinase inhibitor osimertinib in lung adenocarcinoma. Cancer Science. 2021; 112: 3810–3821.
[68] Kang MH, Jeong KJ, Kim WY, Lee HJ, Gong G, Suh N, *et al*. Musashi RNA-binding protein 2 regulates estrogen receptor 1 function in breast cancer. Oncogene. 2017; 36: 1745–1752.
[69] Choi YM, Kim KB, Lee JH, Chun YK, An IS, An S, *et al*. DBC2/RhoBTB2 functions as a tumor suppressor protein via Musashi-2 ubiquitination in breast cancer. Oncogene. 2017; 36: 2802–2812
[70] Li M, Li AQ, Zhou SL, Lv H, Wei P, Yang WT. RNA-binding protein MSI2 isoforms expression and regulation in progression of triple-negative breast cancer. Journal of Experimental & Clinical Cancer Research: CR. 2020; 39: 92.
[71] Haiduk TS, Sicking M, Brücksken KA, Espinoza-Sánchez NA, Eder KM, Kemper B, *et al*. Dysregulated Stem Cell Markers Musashi-1 and Musashi-2 are Associated with Therapy Resistance in Inflammatory Breast Cancer. Archives of Medical Research. 2023; 54: 102855.
[72] Jiang X, Tan J, Wen Y, Liu W, Wu S, Wang L, *et al*. MSI2-TGF-β/TGF-β R1/SMAD3 positive feedback regulation in glioblastoma. Cancer Chemotherapy and Pharmacology. 2019; 84: 415–425.
[73] Dong W, Liu X, Yang C, Wang D, Xue Y, Ruan X, *et al*. Glioma glycolipid metabolism: MSI2-SNORD12B-FIP1L1-ZBTB4 feedback loop as a potential treatment target. Clinical and Translational Medicine. 2021; 11: e411.
[74] Jiang P, Zhang T, Wu B, Li X, Fu M, Xu B. Musashi-2 (MSI2) promotes neuroblastoma tumorigenesis through targeting MYC-mediated glucose-6-phosphate dehydrogenase (G6PD) transcriptional activation. Medical Oncology (Northwood, London, England). 2023; 40: 332.

[75] Zhang W, Li JZ, Tai QY, Tang JJ, Huang YH, Gao SB. LncRNA DANCR regulates osteosarcoma migration and invasion by targeting miR-149/MSI2 axis. European Review for Medical and Pharmacological Sciences. 2020; 24: 6551–6560.
[76] Dong P, Xiong Y, Hanley SJB, Yue J, Watari H. Musashi-2, a novel oncoprotein promoting cervical cancer cell growth and invasion, is negatively regulated by p53-induced miR-143 and miR-107 activation. Journal of Experimental & Clinical Cancer Research: CR. 2017; 36: 150.
[77] Wang R, Liu L, Jiao J, Gao D. Knockdown of MIR4435-2HG Suppresses the Proliferation, Migration and Invasion of Cervical Cancer Cells via Regulating the miR-128-3p/MSI2 Axis in vitro. Cancer Management and Research. 2020; 12: 8745–8756.
[78] Zhao LW, Yu AJ, Zhang YJ, Wang XC, Han B, Wang XH. MicroRNA-149 suppresses the malignant phenotypes of ovarian cancer via downregulation of MSI2 and inhibition of PI3K/AKT pathway. European Review for Medical and Pharmacological Sciences. 2020; 24: 55–64.
[79] Valsecchi L, Naso S, Procopio S, Mauri M, Piazza R, Watrin T, *et al*. The RNA Binding Protein Musashi-2 (MSI2) Sustains the Growth and the Leukemogenic Potential of MLL-Rearranged Acute Lymphoblastic Leukemia, and It Is Involved in Glucocorticoid Resistance. Blood. 2022; 140: 8827–8828.
[80] de Andrés-Aguayo L, Varas F, Graf T. Musashi 2 in hematopoiesis. Current Opinion in Hematology. 2012; 19: 268–272.
[81] MacNicol MC, Cragle CE, McDaniel FK, Hardy LL, Wang Y, Arumugam K, *et al*. Evasion of regulatory phosphorylation by an alternatively spliced isoform of Musashi2. Scientific Reports. 2017; 7: 11503.
[82] Park SM, Deering RP, Lu Y, Patrick T, Shenoy V, Lianoglou S, *et al*. Msi2 Directly Regulates The TGF-β Signaling Pathway and Myeloid Lineage Bias In Hematopoietic Stem Cells. Blood. 2013; 122: 468.
[83] Xue Y, Wang K, Jiang Y, Dai Y, Liu X, Pei B, *et al*. An ultrasensitive and multiplexed miRNA one-step real time RT-qPCR detection system and its application in esophageal cancer serum. Biosens Bioelectron. 2024; 247: 115927.